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Cardiac baroreceptor sensitivity: A prognostic marker in predialysis chronic kidney disease patients?

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Background. Small, uncontrolled studies of dialysis-dependent chronic kidney disease (CKD) patients have demonstrated abnormalities of cardiovascular autonomic control and vascular compliance, which may contribute to adverse cardiovascular morbidity in this population. However, there is little information utilizing newer, noninvasive techniques in predialysis patients with increasing degrees of uremia.

Methods. One hundred and five nondialysis CKD patients with a median GFR of 23 mL/min/1.73m^2 (range: 6 to 102) at baseline were studied. Cardiac baroreceptor sensitivity (BRS) was recorded by time- and frequency-domain techniques, and its relationship with increasing degrees of uremia studied. During a mean follow-up period of 42 months (range: 3 to 70), primary (death, dialysis, transplantation) and secondary (fatal and nonfatal cardiovascular events) outcome measures were recorded. The importance of cardiac BRS in comparison to other important renal and cardiovascular prognostic variables in predicting outcome was assessed.

Results. Median cardiac BRS by time domain analysis at baseline was 8.85 msec/mm Hg (interquartile range: 6.85), and impaired cardiac BRS was related to reduced GFR, increasing age, and hypertension on quantile regression analysis. 'Impaired' cardiac BRS was associated with a trend toward increased likelihood of both primary and secondary outcomes, and may act as a surrogate measure of other cardiovascular risk factors, including age, hyperlipidemia, hypertension, previous cardiovascular disease, and doubling of creatinine.

Conclusion. Nondialysis-dependent CKD patients have impaired cardiac BRS, and this was related to decreasing GFR. There was a trend toward poorer prognosis in patients with impaired cardiac BRS that requires further study. Cardiac BRS may provide a simple, bedside, noninvasive assessment of overall cardiovascular risk in this population.

Key words: uremia, autonomic dysfunction, baroreceptor sensitivity, prognosis.

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Recent studies suggest that autonomic nervous system dysfunction (AD) is associated with an increased risk of mortality in various disease states, including myocardial infarction [1, 2], diabetes [3–5], acute stroke [6], and hypertension or prevalent cardiovascular disease [5]. The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, for example, assessed cardiac baroreceptor sensitivity (BRS) within 28 days of an acute myocardial infarct and demonstrated that low cardiac BRS (<3.0 ms/mm Hg) carried a significant risk of cardiac mortality over a mean follow-up period of 21 months [2]. This effect was independent of left ventricular dysfunction and of ventricular arrhythmias.

In a chronic kidney disease (CKD) population, several studies have demonstrated a higher incidence of cardiac morbidity and mortality in patients with autonomic dysfunction [7–9]. In terms of morbidity, Jassal et al [7] showed an increased incidence of arrhythmias on 24-hour electrocardiograph (ECG) monitoring in hemodialysis patients who had autonomic dysfunction on standard tests. Krivoshiev et al [8] compared the corrected QT interval (QTc) on ECG with the Valsalva test and deep breathing test in 20 hemodialysis patients, and reported a marked negative correlation between the duration of the electrical systole of the heart and the results of the two tests of autonomic function: $R = -0.7058$, $P < 0.001$ between QTc and change of heart rate in deep breathing, and $R = -0.7133$, $P < 0.001$ between QTc and the Valsalva ratio. Citing their experience of seven hemodialysis patients with significantly prolonged QTc intervals who had died of sudden cardiac death, they concluded that uremic neuropathy could predispose to sudden cardiac death by impairing the function of the parasympathetic nervous system. Finally, Tozawa et al prospectively studied 144 hemodialysis patients, and reported a hazard ratio for all-cause mortality that was increased 1.63 times per 1% increase in coefficient of variation in systolic blood pressure (SBP) [9].

However, these studies were based exclusively on dialysis patients, when changes in cardiovascular autonomic control and its consequences may be less amenable to

therapeutic modification. Therefore, it is interesting that Agarwal et al have reported impaired BRS and parasympathetic nervous system dysfunction in 25 CKD patients using invasive methodologies, though this was shortly before their patients became dialysis dependent [10]. Furthermore, Hathaway et al utilized noninvasive frequency domain measures of 24-hour heart rate variability, and reported impaired values in CKD patients compared to controls. Though this study included 43 nondialysis-dependent patients, they nonetheless had advanced renal impairment and were awaiting renal transplantation [11].

To our knowledge, there is little information on cardiovascular autonomic control, as assessed by noninvasive cardiac BRS techniques, in a predialysis CKD population. In particular, the effects of renal impairment on cardiac BRS independent of other cardiovascular variables have not been studied. Furthermore, the association between cardiovascular AD in predialysis patients and prognosis is unclear.

METHODS

Subjects

One hundred and nine predialysis CKD patients were recruited from the outpatient clinics of the University Hospitals of Leicester Nephrology Department between May 1998 and April 2003. For the purposes of study analysis, the study was closed to follow-up of primary and secondary outcome events on March 31, 2004 (census date). The mean duration of follow-up was 42 months (range 3 to 70 months). The following patient groups were excluded from the study: congestive cardiac failure, atrial fibrillation, or unstable vascular disease (defined by any episode of acute coronary syndrome, stroke, or transient ischemic attack in the preceding 6 months); diabetes mellitus, amyloidosis, or any other conditions associated with autonomic neuropathy. Most patients were taking medication, including antihypertensive and statin therapy, with potential cardiovascular and autonomic effects (Table 1). It was not considered ethical to discontinue these medications during baseline assessment of cardiac BRS, and these medications were continued throughout the study period, although the presence or absence of cardiovascular medication was included as a variable in the subsequent statistical analysis.

All subjects gave their informed consent, and the Leicestershire Local Research Ethics Committee approved the study.

Protocol

Height, weight, and body mass index were recorded at the first visit. A baseline glomerular filtration rate was measured by a plasma iodohexol clearance technique [12] in the majority of patients, though this was not possible in 11 patients in whom 24-hour urinary creatinine clearance was used as a surrogate marker. Routine investigation of hemoglobin, creatinine, and total cholesterol was assessed in the week prior to cardiac BRS measurement. In addition, another serum creatinine estimation was recorded at census date, or within six months before census date.

Table 1. Baseline characteristics of study population

Parameter	*N* (%)
Ethnicity	
Caucasian	95 (91)
South Asian	10 (9)
Smoking status: current/ex-smoker	51 (49.5)
Comorbid conditions	
Hypertension	85 (81)
Ischemic heart disease	14 (13)
Other vascular disease	11 (11)
Hyperlipidemia	32 (31)
Causes of chronic kidney disease	
Autosomal polycystic kidney disease	29 (28)
Chronic pyelonephritis/interstitial nephritis	11 (11)
Glomerulonephritis	30 (29)
Hypertension	8 (8)
Renovascular disease	5 (5)
Vasculitis	3 (3)
Other	11 (11)
Unknown	18 (17)
Baseline therapy (at cardiac BRS estimation)	
ACE inhibitor/angiotensin II antagonist	57 (54)
Alpha-blocker	20 (19)
Beta-blocker	32 (31)
Calcium channel antagonist	45 (43)
Diuretic	49 (47)
Aspirin	14 (13)
Statin	26 (25)

On the day of cardiac BRS measurement, all patients attended the cardiovascular laboratory at least 2 hours after a light meal, and having abstained from smoking, alcohol, and caffeinated products for at least 12 hours. Investigations were carried out in a quiet room with an ambient temperature of 20 to 24°C, and patients were asked to micturate prior to the study. After it was determined that there was no interarm difference in BP greater than 10 mm Hg, casual supine BP was measured on three occasions with a standard mercury sphygmomanometer and cuff of appropriate size, and the mean value was used in subsequent analysis. Subjects were fitted with chest leads for continuous ECG recording (model CR7, Cardiac Recorders Limited, London, UK) and the appropriately sized cuff of the 2300 Finapres noninvasive BP monitor (Ohmeda, Englewood, CO, USA). This is a fully automated device that allows continuous noninvasive assessment of finger arterial pressure. It utilizes the arterial clamp technique of Penaz [13] and is well validated against intra-arterial BP measurement in all age groups [14, 15]. The cuff was fitted to the middle finger or thumb of the nondominant arm and maintained at heart level by resting on an adjustable support throughout.

After a resting period of at least 15 minutes, and after achievement of a satisfactory BP signal from the

monitor and the stabilization of BP at the same level (mean 2-minute BP levels not varying by >10 mm Hg over ≥10 min), recordings were performed for three sequential periods of 10 minutes each. The Finapres has a built-in system (Physio-Cal) that briefly interrupts the BP recording automatically to keep the finger arteries fully unloaded and the transmural pressure equal to zero (usually for 2 to 3 beats every 70 beats). This was switched off during the recording period but applied at 10-minute intervals during the monitoring period. Subjects were asked to maintain a respiratory rate >15 breaths per minute, although respiratory rate and tidal volume were not formally measured. The analog outputs from the Finapres and simultaneous surface ECG recordings underwent analog-to-digital conversion at a rate of 200 samples per second, and were downloaded to a dedicated personal computer for subsequent analysis and noninvasive estimation of cardiac BRS.

Patients subsequently continued with their usual follow-up at the nephrology outpatient clinics. Following the close of the study, end points were recorded retrospectively from a number of sources, including hospital medical records, the nephrology department information system (PROTON), and the registrar for births, marriages, and deaths in Leicestershire and Northamptonshire. Causes of death were ascertained from either the coroners' reports or death certificates, completed independently of the study investigators by the patients' attending physician.

Data analysis

Software specially written by the Leicester Warwick Medical School Division of Medical Physics, and which is in routine use in the department in which these studies were undertaken [16], was used in the offline analysis of the beat-to-beat BP and pulse interval (PI) recordings. The derived PI and SBP were analyzed by means of power spectral analysis (PSA) with fast Fourier transform (FFT) with 512 samples. The data segments used were extracted under visual inspection from the most stable (i.e., stationary) segment of each 10-minute recording. The beat-to-beat series of PI and SBP were interpolated with a third-order polynomial and resampled with an interval of 0.5 seconds to produce signals with a uniform time axis. The power spectra were obtained as the average of three recordings for each patient, and were smoothed with a 13-point triangular window. Estimates of power spectra of PI and SBP, coherence function, and frequency response between PI and SBP with 58 degrees of freedom (df) were thus produced. Coherence between BP and PI variability reflects the amount of linear coupling between the two spectra and is, therefore, comparable to the correlation coefficient in regression analysis. A coherence value >0.40 was considered significant [17]. Recordings with an ectopy rate >2% were rejected. (Spikes on the resampled tracings of the PI and SBP recordings were manually removed, and a straight line was interpolated by the computer, although resampled tracings with >4 spikes were excluded from subsequent analysis to avoid bias.) PSA was undertaken to calculate the cardiac BRS as the combined and LF α-index. Cardiac BRS estimation was also made utilizing time-domain analysis techniques, with combined pressor and depressor sequences.

Outcome measures

The primary outcome measure included death and end-stage renal disease, defined by the need for long-term dialysis or renal transplantation. The secondary outcome of fatal and nonfatal cardiovascular events was also recorded, and included a composite of myocardial infarction, new-onset arrhythmias associated with hemodynamic compromise, stroke, hospitalization for angina or heart failure, coronary or other revascularization, and death from cardiovascular causes.

Statistical analysis

Values for the clinical and nonclinical continuous parameters were expressed as mean ± standard deviation. The distribution patterns of all the parameters were explored using the box plot and normal Q-Q plot. We have used the quantile regression technique (QR), while exploring the association of cardiac BRS with the various clinical parameters. The generalized linear regression (GLS) and even regression models with nonlinear transformations did not provide good fit, the problems of nonnormality of regression residuals and heteroscedasticity being evident in the course of model fitting. The QR is a nonparametric statistical technique based on conditional quantile functions, whereas the classic linear regression methods based on minimizing sums of squared residuals enables us to estimate models for conditional mean functions [18, 19]. Five quantiles were used to obtain the best-fitted regression model, and the computations were carried out using SPLUS 6.1 (Insightful Corporation, USA) and SHAZAM (SHAZAM Project, University of British Columbia, Vancouver, Canada) computation software.

To explore the influence of various risk factors on outcomes, the multiple logistic regression technique was used, and the influential risk factors in the models were introduced following 'step-wise' technique. The Cox regression technique with 'step-wise' selection of risk factors was employed to assess the survival patterns for both primary and secondary outcomes, and the inclusion of various risk factors in the regression models was based on the likelihood ratio criteria. The Kaplan-Meier estimates were obtained for primary and secondary outcomes, with factors differentiating between 'normal' and

Table 2. Baseline clinical and laboratory parameters of study population

Parameter	Mean (SD)
Hemoglobin *g/dL*	13.19 (1.91)
Serum creatinine *μmol/L*	282.75 (173.48)
Total cholesterol *mmol/L*	5.64 (1.05)
Clinic systolic blood pressure *mm Hg*	134 (14)
Clinic diastolic blood pressure *mm Hg*	80 (8)
Body mass index kg/m^2	27.66 (4.37)
Stage of chronic kidney disease [20][a]	
Stage 1: GFR >90 mL/min/1.73m^2	1 (1)
Stage 2: GFR 60 to 89	12 (11)
Stage 3: GFR 30 to 59	27 (26)
Stage 4: GFR 15 to 29	39 (37)
Stage 5: GFR <15	24 (23)
Cardiac BRS by CKD stage *msec/mm Hg*	
Stage 1	11.27 (1 patient only)
Stage 2	11.25 (6.67)
Stage 3	12.96 (6.67)
Stage 4	10.63 (7.83)
Stage 5	8.22 (5.80)

Cardiac baroreceptor sensitivity calculated by combined α-index. All data are presented as mean (standard deviation), except [a]number (%).

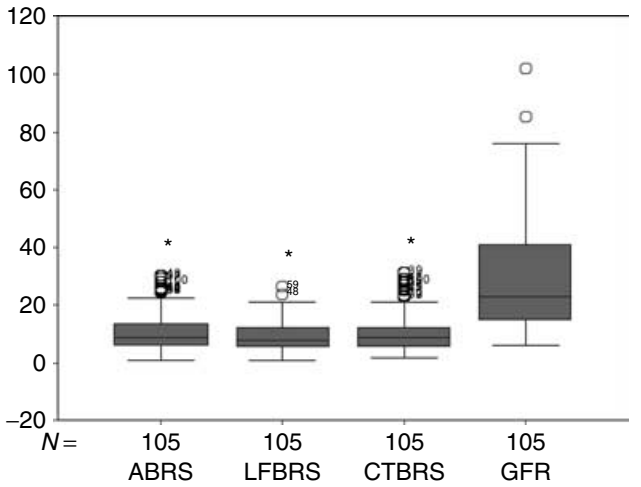

Fig. 1. Box plots of the cardiac baroreceptor sensitivity measurements and glomerular filtration rate. All techniques: ABRS, combined α-index BRS; LFBRS, low frequency BRS; CTBRS, combined time-domain BRS (msec/mm Hg) and GFR (mL/min/1.73 m^2).

'impaired' levels of cardiac BRS (as assessed by combined pressor and depressor sequences). Cardiac BRS was dichotomized at the median value for the study population as described previously [2, 6]: 'normal' ≥median, 'impaired' <median. The survival plots were based on the Kaplan-Meier analysis, and the log rank test was used to test for differences between survival curves. In all statistical procedures, a *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

One hundred and nine patients were recruited to this study between May 1998 and April 2003 from the outpatient clinics of the University Hospitals of Leicester NHS Trust Nephrology Department, although four patients were subsequently excluded following data analysis due to interference from ectopic beats in the derivation of BRS indices. In total, 105 patients (74 male) of median age 57 years (range: 24–80) were included in the study, and relevant demographic information is presented in Table 1. Most patients had a history of hypertension (81%), and were taking vasoactive medication during the study period (Table 1). While predialysis CKD patients were recruited with a range of renal impairment, the distribution of GFR was highly positively skewed (coefficient of skewness: 1.82), with 65 patients having a GFR <30 mL/min (Table 2). Details of other baseline clinical parameters, including creatinine, hemoglobin, total cholesterol, and casual SBP and DBP, are presented in Table 2.

Baseline levels of median (IQR) cardiac BRS were 8.85 (6.85), 7.67 (7.05), and 8.78 (7.38) msec/mm Hg, calculated by combined pressor and depressor sequences, LF α-index, and combined α-index, respectively. The existence of outliers and skewed patterns in the distribution of BRS measurements and GFR by all techniques can be observed in Figure 1. The relation of BRS with other common risk factors, including age and BP, is known to be nonlinear. The relationship between BRS and impaired renal function, as measured by GFR, was assessed by both parametric and nonparametric regression techniques. The Spearman's rank correlation coefficients between GFR and cardiac BRS were significant for the combined pressor and depressor (0.30) and combined α-index (0.27) measurements only, at the 1% level. In addition, the patterns of relationships between GFR and all BRS measurements were explored using the nonparametric kernel smoothing technique. It can be seen that the relationships were of a similar pattern (Fig. 2). Regression fits for all measurements of cardiac BRS (with stepwise selection of all possible factors) suggested the presence of heteroscedasticity and non-normality in error distribution. Quantile regression techniques with logarithmic transformation of cardiac BRS gave the best possible fits, among various linear and nonlinear (Box-Cox transformation) alternatives. The regression estimates are presented in Table 3. Logarithmically transformed cardiac BRS was significantly associated with GFR for combined pressor and depressor and LF α-index measures, but not with the combined α-index technique (Table 3). Clinic SBP, age, and BMI were significantly negatively associated with all measures of cardiac BRS (Table 3), the selection of covariates in these regression analyses being based on the statistical model fit criteria [18]. In addition, the patterns of the residuals from the regression fits were explored, and the estimates of the variances and the coefficients of skewness (SK) of the regression residuals are presented in Table 3. All three models fitted well with very small coefficients of skewness for the regression residuals and low standard errors (SE).

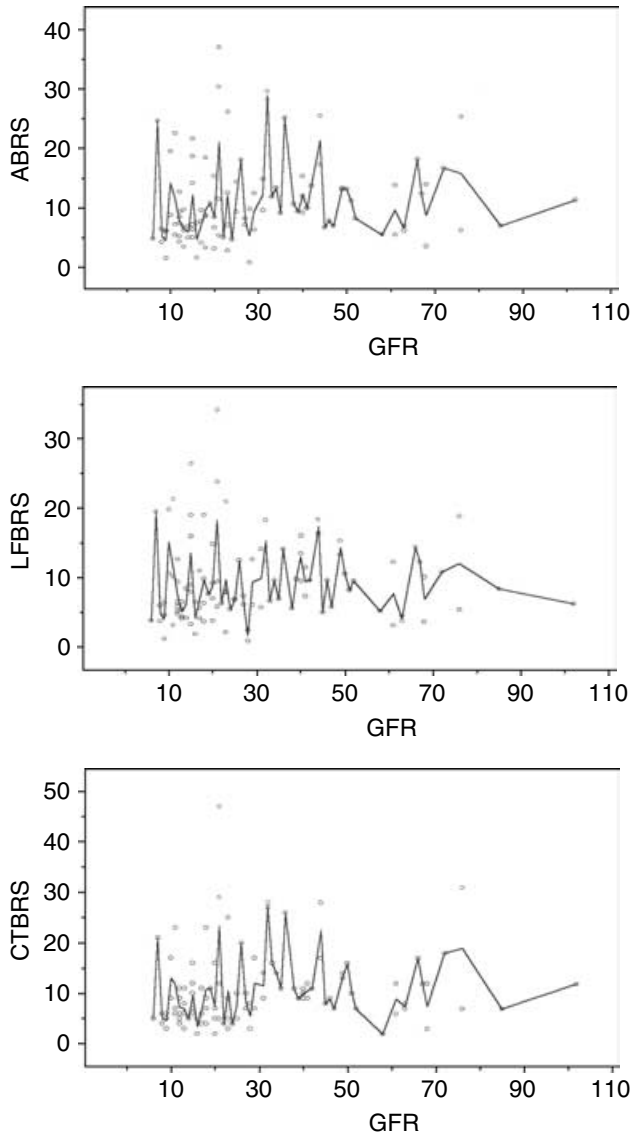

Fig. 2. Plot of the relationship between glomerular filtration rate and all measures of cardiac baroreceptor sensitivity using kernel smoothing technique: (*A*) combined α-index (ABRS), (*B*) LF α-index (LFBRS), (*C*) sequence BRS (CTBRS).

Over the mean study follow-up period of 42 months (range, 3 to 70 months), there was an expected deterioration in renal function with a mean creatinine at study census date of 405 (SD: 297) μmol/L (GFR measurements were not repeated). In total, 16 (15.2%) patients doubled their creatinine during the follow-up period. Forty-six primary outcome events were recorded: 8 deaths (7.6%), 27 dialysis (25.7%), and 11 transplantations (10.5%). The significance of various risk factors in predicting primary outcome events was explored using multiple logistic regression techniques; with a model including total cholesterol [odds ratio (OR) = 7.43, 95% CI = 1.09 to 35.38, $P = 0.03$), age (OR = 1.05, 95% CI = 0.95 to 2.95, $P = 0.02$), history of cardiovascular event (OR = 2.93, 95% CI = 1.80 to 6.23, $P = 0.01$), and census creatinine (OR = 1.02, 95% CI = 1.07 to 1.20, $P < 0.001$), correctly predicting 97.4% of combined primary outcome of death, dialysis, and transplantation. A secondary outcome of fatal or nonfatal cardiovascular event was recorded in 13 patients: 5 fatal (1 stroke, 1 acute myocardial infarction, 2 cardiac failure secondary to ischemic heart disease, 1 sudden death) and 13 nonfatal (3 stroke/TIA, 2 acute coronary syndromes, 3 coronary revascularization, 1 renal angioplasty, 1 atheroembolic episode, 1 pulmonary embolism, 1 arryhythmia with hemodynamic compromise, and 1 ischemic bowel).

The analyses of the survival patterns for both primary and secondary outcomes were performed separately by stratifying the patients by 'impaired' (<median) and 'normal' (≥median) cardiac BRS [2, 6] using the combined pressor and depressor sequence method. Results of the Kaplan-Meier survival time analysis are presented in Table 4. Though the survival times to either death, dialysis, and transplantation (primary outcome) or fatal and nonfatal cardiovascular event (secondary outcome) are lower in the group of predialysis CKD patients with 'impaired' cardiac BRS, the survival distribution patterns do not differ significantly between those with 'impaired' compared to 'normal' cardiac BRS (Table 4, Fig. 3). Of note, median survival time to primary outcome is significantly lower by 30.5 months in patients with doubling of creatinine during the follow-up period (log-rank, P value < 0.001, data not shown). Finally, the results obtained from the Cox regression for both primary and secondary outcomes are presented in Table 5. The final model and the variable selection are based on the log likelihood ($Ln\ L$) criteria. In particular, higher total cholesterol and clinic SBP, history of previous cardiovascular event, and presence of doubling of creatinine are significantly associated with the risk of death, dialysis, or transplantation, while higher hemoglobin levels are associated with a reduced risk (Table 5).

DISCUSSION

The present study has reported for the first time in a predialysis CKD population that increasing impairment of renal function as assessed by GFR is associated with impaired cardiovascular autonomic control as assessed noninvasively by cardiac BRS measurements using time- and frequency-domain techniques. Furthermore, when the study population was dichotomized into groups with 'impaired' and 'normal' cardiac BRS, even in this small study there was a trend toward poor prognostic outcome in the 'impaired' cardiac BRS group, in terms of progression to death, dialysis, and transplantation or the occurrence of fatal and nonfatal cardiovascular events. However, recognized markers of poor cardiovascular prognosis were more clearly associated with poor

Table 3. Quantile regression results for cardiac baroreceptor sensitivity

Criterion	Sequence BRS[a]		Combined α-index		LF α-index	
	Est.	*P* value	Est.	*P* value	Est.	*P* value
Age	−0.23	<0.001	−0.21	<0.001	−0.19	<0.001
Body mass index	−0.34	<0.001	−0.28	<0.001	−0.11	<0.001
GFR	0.01	<0.001	0.003	0.10	0.03	<0.001
Clinic SBP	−0.08	<0.001	−0.06	<0.001	−0.09	<0.001
Residual variance	0.81	0.99	0.95			
SK (SE)	0.11 (0.54)		−0.62 (0.53)		−0.51 (0.48)	

[a]Combined pressor and depressor sequences.

Table 4. Kaplan-Meier estimates for primary and secondary outcomes in predialysis chronic kidney disease patients with 'normal' and 'impaired' cardiac baroreceptor sensitivity (assessed by combined pressor and depressor sequence analysis)

	Primary outcome		Secondary outcome	
	'Impaired'	'Normal'	'Impaired'	'Normal'
Total (number of events)	52 (21)	53 (15)	52 (8)	53 (5)
Mean survival time (SE)	52.0 (2.8)	57.7 (2.5)	61.6 (2.6)	63.7 (2.1)
95% confidence intervals	46.4–57.5	52.8–62.6	56.5–66.7	59.7–67.8
Median survival time (SE)	61.0 (10.1)	64.5 (3.8)	63.5 (17.4)	67.5 (3.8)
95% confidence intervals	41.3–80.7	57.0–72.0	33.4–101.7	40.0–92.0
Log-rank *P* value	0.10		0.28	

Primary outcome is death, dialysis, and transplantation, and secondary outcome is fatal and nonfatal cardiovascular events. Survival time is expressed in months.

outcome using Cox regression techniques, including age, hypertension, hyperlipidemia, previous vascular disease, and creatinine doubling, although cardiac BRS may act as a simple, noninvasive, bedside assessment of a patient's overall cardiovascular risk, as in other populations [33]. Importantly, this simple test may identify 'at risk' predialysis CKD patients, where more aggressive risk factor manipulation may improve cardiovascular prognosis.

Impaired cardiac BRS has previously been reported in CKD patients, and has been one factor implicated in intradialytic hypotension [10, 21–26]. However, these studies have predominantly used invasive methods to assess BRS in small populations of hemodialyzed patients. In the only comparable study, Agarwal et al reported a significantly reduced BRS of 3.88 msec/mm Hg in 25 nondialysis-dependent CKD patients compared to controls [10]. However, the study was of young patients with a mean age of 28.5 years. Also, this study estimated BRS using an invasive pressor method with phenylephrine, while the present study assessed BRS from spontaneous fluctuations in BP and PI measured noninvasively. A further advantage of this technique are the powers of the various components of the decomposed spectra of SBP and PI variability can be compared, and this allows an assessment of the integrity of the underlying sympathovagal balance of autonomic cardiovascular system control [27, 28]. Converse et al have reported increased sympathetic nerve discharge in hemodialysis-dependent CKD patients, although formal studies of sympathetic activity were not performed in the present study [34]. In keeping with previous studies of hemodialysis-dependent CKD patients [10, 21, 29–32], the present study reports impaired cardiac BRS in a predialysis CKD population. Indeed, a similar result was found whether cardiac BRS was assessed from the combined pressor and depressor sequences (time-domain) or from spontaneous fluctuations in BP and PI (frequency-domain). A significant relationship using frequency-domain techniques was only found for cardiac BRS calculated from the α-index in the LF band. However, this is more likely to indicate baroreceptor dysfunction because the combined α-index includes the HF band, where there may be respiratory effects [28].

Such changes in cardiac BRS may be of prognostic significance. Certainly, autonomic dysfunction has been implicated in cardiovascular morbidity and mortality secondary to cardiac dysrhythmias following acute myocardial infarction [2] and cerebrovascular disease [6]. The present study reports a trend toward poor outcome in predialysis CKD patients, whether for the primary outcome of death, dialysis, and transplantation or the secondary outcome of fatal and nonfatal cardiovascular events. However, these trends were not significant, and indeed, other vascular and renal risk factors were significant on Cox regression analysis, including age, hyperlipidemia, hypertension, a history of cardiovascular events, and the presence of creatinine doubling. Interestingly, other groups have reported similar findings in hypertensive patients, and have suggested that the measurement of cardiac BRS may act as a surrogate for the assessment of multiple risk factors in a population at vascular risk [33].

However, our small study has a number of important limitations. First, it is clearly important to confirm these findings in a larger population over a longer follow-up period. Also, it would be important to determine that it is possible to modify outcome by using such techniques to identify a higher risk predialysis CKD population that

Table 5. Cox regression results for primary and secondary outcomes

	Primary outcome			Secondary outcome		
Parameter	Est. β (SE)	*P* value	Exp. β (95% CI)	Est. β (SE)	*P* value	Exp. β (95% CI)
Age				0.16 (0.05)	0.003	1.18 1.06, 1.31
Cardiovascular event	0.75 (0.23)	0.001	2.11 1.34, 3.34			
Clinic SBP	0.04 (0.01)	0.01	1.04 1.01, 1.07			
Creatinine				0.003 (0.001)	0.008	1.003 1.00, 1.01
Double creatinine	0.55 (0.20)	0.006	1.74 1.17, 2.58			
Hemoglobin	−0.35 (0.1)	0.007	0.71 0.55, 0.91			
Smoking history				2.09 (0.91)	0.02	8.09 1.36, 48.1
Total cholesterol	0.41 (0.19)	0.04	1.50 1.03, 2.20			
Other vascular disease				−2.27 (0.89)	0.01	0.10 0.12, 0.59
−2 Ln L		217.0			54.5	

Primary outcome is death, dialysis, and transplantation, and secondary outcome is fatal and nonfatal cardiovascular events.

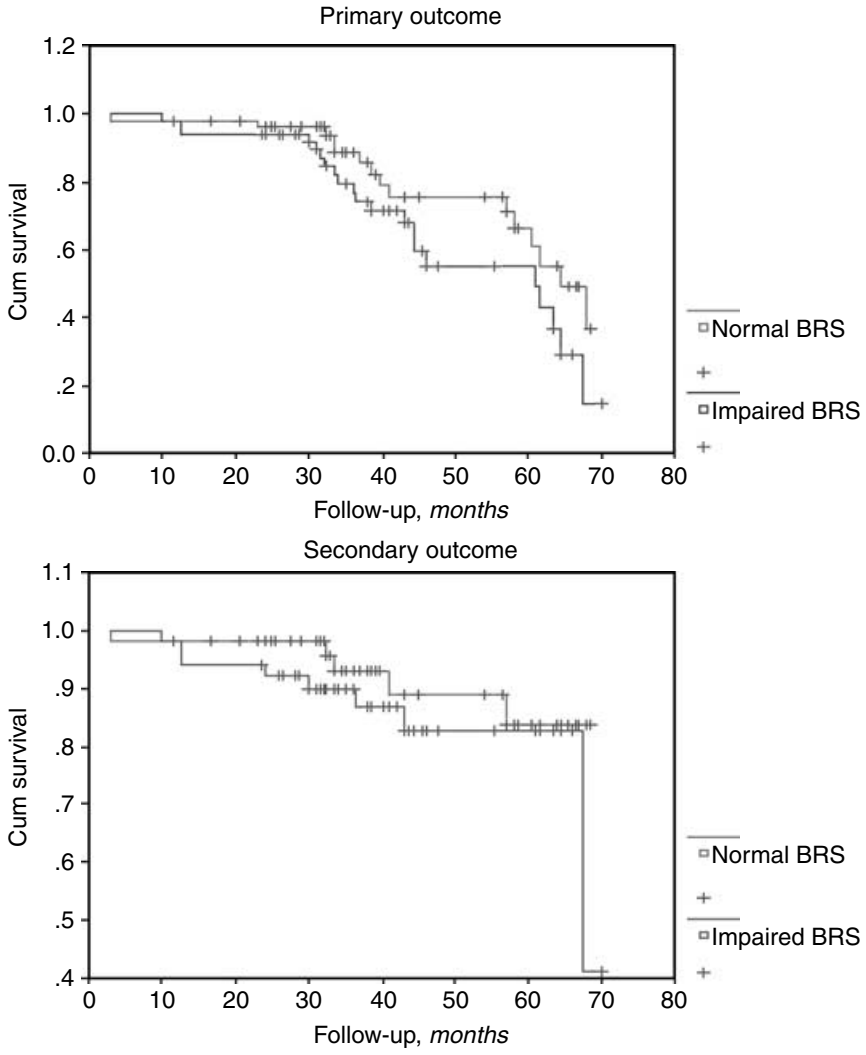

Fig. 3. Kaplan-Meier survival plots for (*A*) primary and (*B*) secondary outcomes, stratified by 'normal' and 'impaired' cardiac baroreceptor sensitivity (assessed by the combined pressor and depressor sequence analysis technique).

is targeted with aggressive multifaceted risk factor modification therapies. Second, many patients were on cardiovascular drugs with the potential to influence cardiac BRS, including ACE inhibitors, beta- and alpha-blockers, and statin therapy. However, for practical and ethical reasons, it was not felt appropriate to discontinue therapy for the purpose of conducting the study. Nonetheless, no statistically significant differences were found in cardiac BRS between patients prescribed beta-blockers and those not for all measures of cardiac BRS; sequence BRS: 10.77 (9.32) versus 10.16 (6.68) msec/mm Hg, combined α-index BRS: 11.72 (8.22) versus 10.37 (6.48), LF α-index BRS: 9.78 (7.66) versus 9.08 (5.03), respectively. Finally, the echocardiographic assessment of left ventricular hypertrophy would have been a better assessment of cardiovascular risk rather than the presence of hypertension, per se, although unfortunately, left ventricular mass index was not calculated on all patients.

CONCLUSION

Cardiovascular disease is the leading cause of death in CKD patients [35]. Previous studies have reported abnormalities of reduced BRS to be associated with increased mortality, particularly cardiovascular, in dialysis-dependent CKD patients. Importantly, our preliminary observations extend this relationship between impaired renal function (GFR) and BRS to a predialysis CKD population, and indicate that impaired cardiac BRS may be a simple marker of increased risk. However, it remains to be demonstrated if therapeutic interventions to modify known cardiovascular risk factors could lead to an improvement in cardiac BRS, and will improve cardiovascular outcomes in predialysis CKD patients.

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